AMENDMENT TO THE SPECIFICATION

Please replace the paragraph beginning at page 4, line 3, with the following rewritten paragraph:

Within one aspect of the present invention, isolated nucleic acid molecules are provided, wherein said nucleic acid molecules are selected from the group consisting of: (a) an isolated nucleic acid molecule comprising sequence ID Nos. 1, 5, 7, 9, 11, 13, or, 15, or complementary sequence thereof; (b) an isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of (a) under conditions of high stringency; and (c) an isolated nucleic acid that encodes a TGF-beta binding-protein according to (a) or (b). Within related aspects of the present invention, isolated nucleic acid molecules are provided based upon hybridization to only a portion of one of the above-identified sequences (e.g., for (a) hybridization may be to a probe of at least 20, 25, 50, or 100 nucleotides selected from nucleotides 156 to 539 or 555 to 687 of Sequence ID No. 1). As should be readily evident, the necessary stringency to be utilized for hybridization may vary based upon the size of the probe. For example, for a 25-mer probe high stringency conditions could include: 60 mM Tris pH 8.0, 2 mM EDTA, 5x Denhardt's, 6x SSC, 0.1% (w/v) N-laurylsarcosine, 0.5% (w/v) NP-40 (~~n~~Nonidet P-40) overnight at 45 degrees C, followed by two washes with 0.2x SSC / 0.1% SDS at 45-50 degrees. For a 100-mer probe under low stringency conditions, suitable conditions might include the following: 5x SSPE, 5x Denhardt's, and 0.5% SDS overnight at 42-50 degrees, followed by two washes with 2x SSPE (or 2x SSC) /0.1% SDS at 42-50 degrees.

Please replace the paragraph beginning at page 74, line 6, with the following rewritten paragraph:

The ~200 kilobase (kb) BAC clone 15G5, isolated from the CITB mouse genomic DNA library (distributed by Research Genetics, Huntsville, AL) was used to determine the complete sequence of the mouse *Beer*

gene and its 5' and 3' flanking regions. A 41 kb SalI fragment, containing the entire gene body, plus ~17 kb of 5' flanking and ~20 kb of 3' flanking sequence was sub-cloned into the BamHI site of the SuperCosI cosmid vector (Stratagene, La Jolla, CA) and propagated in the *E. coli* strain DH10B. From this cosmid construct, a 35 kb MluI - AvilI restriction fragment (Sequence No. 6), including the entire mouse *Beer* gene, as well as 17 kb and 14 kb of 5' and 3' flanking sequence, respectively, was then gel purified, using conventional means, and used for microinjection of mouse zygotes (DNX Transgenics; US Patent No. 4,873,191). Founder animals in which the cloned DNA fragment was integrated randomly into the genome were obtained at a frequency of 5-30% of live-born pups. The presence of the transgene was ascertained by performing Southern blot analysis of genomic DNA extracted from a small amount of mouse tissue, such as the tip of a tail. DNA was extracted using the following protocol: tissue was digested overnight at 55°C in a lysis buffer containing 200 mM NaCl, 100 mM Tris pH8.5, 5 mM EDTA, 0.2% SDS and 0.5 mg/ml Proteinase K. The following day, the DNA was extracted once with phenol/chloroform (50:50), once with chloroform/isoamylalcohol (24:1) and precipitated with ethanol. Upon resuspension in TE (10mM Tris pH7.5, 1 mM EDTA) 8-10 ug of each DNA sample were digested with a restriction endonuclease, such as EcoRI, subjected to gel electrophoresis and transferred to a charged nylon membrane, such as HyBond™N+ (Amersham, Arlington Heights, IL). The resulting filter was then hybridized with a radioactively labeled fragment of DNA deriving from the mouse *Beer* gene locus, and able to recognize both a fragment from the endogenous gene locus and a fragment of a different size deriving from the transgene. Founder animals were bred to normal non-transgenic mice to generate sufficient numbers of transgenic and non-transgenic progeny in which to determine the effects of *Beer* gene overexpression. For these studies, animals at various ages (for example, 1 day, 3 weeks, 6 weeks, 4 months) are subjected to a number of different assays designed

to ascertain gross skeletal formation, bone mineral density, bone mineral content, osteoclast and osteoblast activity, extent of endochondral ossification, cartilage formation, etc. The transcriptional activity from the transgene may be determined by extracting RNA from various tissues, and using an RT-PCR assay which takes advantage of single nucleotide polymorphisms between the mouse strain from which the transgene is derived (129Sv/J) and the strain of mice used for DNA microinjection [(C57BL5/J x SJL/J)F2].

Please replace the paragraph beginning at page 77, line 21, with the following rewritten paragraph:

17-nucleotide antisense oligonucleotides are prepared in an overlapping format, in such a way that the 5' end of the first oligonucleotide overlaps the translation initiating AUG of the Beer transcript, and the 5' ends of successive oligonucleotides occur in 5 nucleotide increments moving in the 5' direction (up to 50 nucleotides away), relative to the Beer AUG. Corresponding control oligonucleotides are designed and prepared using equivalent base composition but redistributed in sequence to inhibit any significant hybridization to the coding mRNA. Reagent delivery to the test cellular system is conducted through cationic lipid delivery (P.L. Felgner, *Proc. Natl. Acad. Sci. USA 84*:7413, 1987). 2 ug of antisense oligonucleotide is added to 100 ul of reduced serum media (Opti-MEM® I reduced serum media; Life Technologies, Gaithersburg MD) and this is mixed with Lipofectin® reagent (6 ul) (Life Technologies, Gaithersburg MD) in the 100 ul of reduced serum media. These are mixed, allowed to complex for 30 minutes at room temperature and the mixture is added to previously seeded MC3T3E21 or KS483 cells. These cells are cultured and the mRNA recovered. Beer mRNA is monitored using RT-PCR in conjunction with Beer specific primers. In addition, separate experimental wells are collected and protein levels characterized through western blot methods described in Example 4. The cells are harvested, resuspended in lysis

buffer (50 mM Tris pH 7.5, 20 mM NaCl, 1mM EDTA, 1% SDS) and the soluble protein collected. This material is applied to 10-20 % gradient denaturing SDS PAGE. The separated proteins are transferred to nitrocellulose and the western blot conducted as above using the antibody reagents described. In parallel, the control oligonucleotides are added to identical cultures and experimental operations are repeated. Decrease in Beer mRNA or protein levels are considered significant if the treatment with the antisense oligonucleotide results in a 50% change in either instance compared to the control scrambled oligonucleotide. This methodology enables selective gene inactivation and subsequent phenotype characterization of the mineralized nodules in the tissue culture model. strain of mice used for DNA microinjection [(C57BL5/J x SJL/J)F2].